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10/538,922	06/07/2006	Philippe Boutin	Q88618	5674

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EXAMINER	
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ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/538,922	BOUTIN ET AL.	
	Examiner	Art Unit	
	STEPHEN KAPUSHOC	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 February 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,4 and 6-22* is/are pending in the application.

4a) Of the above claim(s) *3,4 and 6-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 February 2009* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 3, 4, and 6-22 are pending.
Claims 2 and 5 are cancelled.
Claims 3, 4, and 6-22 are withdrawn from examination as detailed below.
Claim 1 is examined on the merits.

Please note: The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

This Office Action is in reply to Applicants' correspondence of 02/23/2009.
Applicants' remarks and amendments have been fully and carefully considered but are not found to be sufficient to put the application in condition for allowance. Any new grounds of rejection presented in this Office Action are necessitated by Applicants' amendments. Any rejections or objections not reiterated herein have been withdrawn in light of the amendments to the claims or as discussed in this Office Action.
This Action is made **FINAL**.

Withdrawn Objection to the Drawings

1. The objection to the drawings, as set forth on page 3 of the Office Action of 10/23/2008, is **WITHDRAWN** in light of the amendments to the drawings. The drawings were received on 02/23/2009. These drawings are accepted.

Withdrawn Objection to the Specification

2. The objections to the disclosure, as set forth on pages 3-4 of the Office Action of 10/23/2008, are **WITHDRAWN** in light of the amendments to the specification, which are entered.

Withdrawn Objection to the Specification - Sequence Compliance

3. The objection to the specification for failure to comply with the Sequence Rules, as set forth on pages 4-5 of the Office Action of 10/23/2008, is **WITHDRAWN** in light of the amendments to the specification.

Withdrawn Claim Objections

4. The Objections to claims 1 and 5, as set forth on page 5 of the Office Action of 10/23/2008, are **WITHDRAWN** in light of the amendments to claim 1and the cancellation of claim 5.

Withdrawn Claim Rejections - 35 USC § 112 2nd ¶ - Indefiniteness

5. The rejections of claim 5under 35 USC 112 2nd ¶, as set forth on pages 5-6 of the Office Action of 10/23/2008, is **WITHDRAWN** in light of the cancellation of claim 5.

Maintained Claim Rejections - 35 USC § 112 1st ¶ - Enablement

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claim 1 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Nature of the invention and breadth of the claims

The claims are drawn to methods for diagnosing a predisposition for morbid obesity in a human subject comprising determining whether there is a -243 A>G alteration in the 5' flanking region of the gad2 gene.

The nature of the claimed invention thus requires knowledge of a correlative association between nucleotide content and a predisposition for obesity.

Direction provided by the specification and working example

The instant specification teaches an analysis of polymorphic nucleotide content in the gad2 gene in obese subjects. The specification teaches an analysis of 369 morbidly obese patients (p.13, p.14) and asserts that the -243 G allele, the -1.6kb A allele, and the -2004 T allele are associated with obesity (Table 1) as compared to 381 control subjects. However, it is noted that the data presented in the instant specification does not provide a consistent statistically significant association between the nucleotide content at the -1.6kb and -2004 positions and morbid obesity in the patient populations that were analyzed.

The specification further teaches (p.17) the analysis of haplotype comprising 'alleles of SNP +61450 C>A, and +83897 T>A' and asserts that haplotype of -243, +61450, +83897 ACT is significantly present in non-obese subjects. However, the instant specification does not provide any sequence context that indicates the position or content of the requirements for detecting the +61450 or +83897 SNP positions.

State of the art, level of skill in the art, and level of unpredictability

While the state of the art with regard to the detection of variation in any given nucleic acid sequence is high, the unpredictability with regard to the association of any

particular variation with a particular phenotype, or the identification of any nucleotide sequence has having a particular functionality, is even higher. Such unpredictability, particularly relevant to the claimed methods, is demonstrated by the post-filing art.

And while the claims broadly require determining the presence of any form of the claimed biallelic -243 SNP in the diagnosis of a predisposition to morbid obesity, it is relevant to point out that it is unpredictable if even the particular associations asserted in the specification (i.e. the -243 G allele, the -1.6kb A allele, and the -2004 T allele are associated with obesity) would be robust, reliable, or reproducible in any population. Initially it is relevant to point out that the instant specification does not provide consistent statistically significant associations between the -1.6bk and -2004 alleles and obesity. Thisted (1998) provides guidance as to what is required to indicate that an association is statistically significant. Thisted teaches that it has become scientific convention to say that a P-value of 0.05 is considered significant (p.5 - What does it mean to be 'statistically significant'), and that values above the conventional reference point of p=0.05 would not be considered strong enough for the basis of a conclusion.

Furthermore, with regard to the other polymorphic positions disclosed in the specification and recited in the instant claims, the post-filing art indicates a lack of significant association with obesity in several study populations. Swarbick et al (2005) teaches an analysis of the -243 polymorphic position comprising two different study populations, and fails to find any significant correlations with obesity. Additionally, Hunt et al (2006) fails to find any significant correlation between three SNPs in the gad2 gene, including the -243 polymorphic position, and obesity in a large study population.

It is thus highly unpredictable as to whether or not one may extrapolate the asserted results obtained with the study subjects of the instant application to any other different group of subjects or any other individual subject.

Quantity of experimentation required

A larger and prohibitive amount of experimentation would be required to make and use the claimed invention. Such experimentation would require case:control analysis of any study population of interest to establish whether or not any form of the biallelic -243 SNP position is in fact associated with a predisposition to morbid obesity. Even if such experimentation were to be performed, there is no assurance that any reliable and robust associations would in fact be identified. In fact, in view of the post filing art, which includes analyses of large populations (i.e.: Hunt et al examines a population comprising 855 morbidly obese subjects; and Swarbrick et al provides a meta analysis comprising 1,252 morbidly obese subjects), it appears that one would not expect the -243 polymorphism to be associated with morbid obesity in any subject population.

Conclusion

After consideration of the teaching of the specification and the specific working examples, considering the breadth of the claims, and the unpredictability in the art, it is the conclusion that an undue amount of experimentation would be required to make and use the invention.

Response to Remarks

Applicants have traversed the rejection of claims under 35 USC 112 1st ¶ for lack of enablement. Applicants' arguments (p. 11-14 of the Remarks of 02/23/2009) have been fully and carefully considered but are not found to be persuasive. Initially it is noted that in light of the amendments to the claims to require that a mutation is indicative of a predisposition to morbid obesity, the portion of the rejection regarding genetic heterogeneity of different type of obesity (i.e.: cited reference of Ohshiro et al) as set forth in the previous Office Action is withdrawn.

Applicants have argued that it is already established in the art that the GAD2 gene is closely associated with morbid obesity (p.12 of the Remarks) and that the instant specification discloses that the mutation at -243 A>G alters gene expression as demonstrated by a luciferase assay. The arguments are not persuasive to withdraw the rejection. The claimed method requires that a particular mutation (i.e.: -243 A>G) is indicative of a predisposition to morbid obesity; the claims are not drawn to any effect on transcription. Thus while applicants argue that the art establishes that the GAD2 gene is associated with the phenotype, at issue with the claimed method is not whether the gene as a whole plays a role in the phenotype, but whether or not a single particular position within the gene can in fact diagnose a predisposition to the phenotype. While the human GAD2 gene encompasses approximately 88kb on chromosome 10, the claims require that a specific nucleotide alteration is indicative of morbid obesity, and while the art may establish that the gene plays a role in the phenotype, the Examiner maintains that the cited art of Swarbick et al and Hunt et al indicate that this required position is not associated with morbid obesity is numerous distinct populations.

Similarly, while the specification may assert that in a transient transfection assay the -243 A>G position effects transcription of a heterologous reporter gene, the claims are not drawn to any levels of or effects on gene transcription. The claims are drawn to a method requiring an association between content at the -243 A>G position and predisposition to morbid obesity; neither the specification nor the art establish that any alleged altered level of transcription caused by content at the -243 A>G position is sufficient to effect onset of morbid obesity, and the Examiner again points to the cited art of Swarbick et al and Hunt et al which indicate that this position is not associated with morbid obesity is numerous distinct populations.

In the examination of the claimed method the Examiner reiterates the teachings of the post-filing art of both Hunt et al and Swarbrick et al. In contrast otht einstant specification, the cited references analyze more cases (e.g.: Hunt et al includes 855 cases) and more different populations including larger populations of subjects (e.g.: Swarbick et al includes German, US, and Canadian populations; and includes a meta-analysis of multiple population studies available in the art) to arrive at the conclusion that there is no reliable association between the -243 A>G position and predisposition to morbid obesity. As such, given the teachings of the specification and the teachings of the cited art, the preponderance of evidence supports the Examiner's conclusion that the specification is not enabling for the association required by the claimed method.

The rejection as set forth is **MAINTAINED**.

Conclusion

8. No claim is allowed.

No new ground(s) of rejection are presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Kapushoc whose telephone number is 571-272-3312. The examiner can normally be reached on Monday through Friday, from 8am until 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached at 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Stephen Kapushoc/
Art Unit 1634